

Stereochemistry

Dr. Dattatray R. Chandam

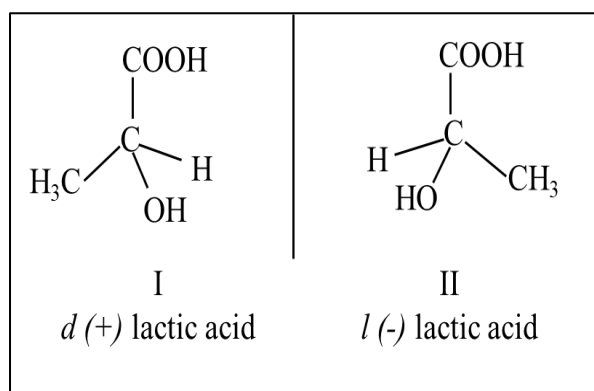
Stereochemistry is a branch of chemistry which deals with arrangements of the atoms of polyatomic molecule in three-dimensional space. The isomerism caused by variation in the arrangement of the atoms or group of atoms in a space is called as stereoisomerism. The isomers having same molecular formula but different orientation of the groups in space is called as stereoisomers. There are three types of stereoisomers; optical, geometrical and conformational isomers. Optical and geometrical isomers are also called as configurational isomers.

Optical isomerism

The stereoisomers having same physical and chemical properties but different action towards plane polarized light is called as optical isomers. The phenomenon that generates optical isomers is called as optical isomerism. The phenomenon of rotating plane of plane polarized light is called as optical activity. A substance which rotates plane of plane polarized light is called as optically active substance. The extent of rotation is measured in “polarimeter” and expressed as specific rotation, denoted by $[\alpha]$.

Let's us consider the example of lactic acid $\text{CH}_3\text{C}^*(\text{H})\text{OHCOOH}$.

It is a chiral molecule (* is on chiral carbon) having 2^{nd} carbon attached to four different groups. It possesses two isomeric forms according to 2^n rule, where n indicates number of chiral centers.



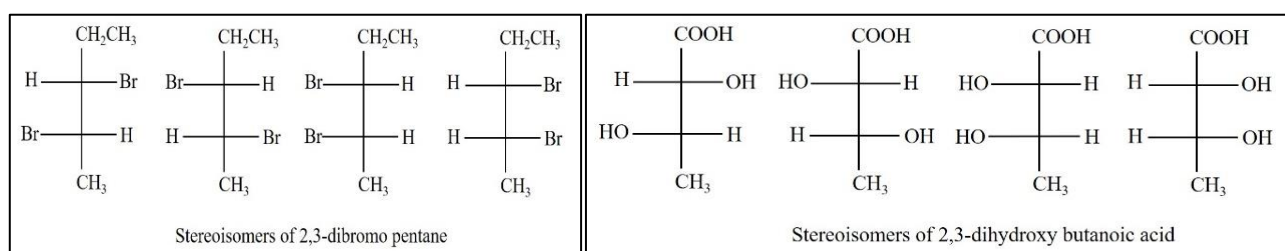
Structure I and II are mirror images of each other. They are non-super imposable, so they are called as enantiomers. One isomer that rotate of plane polarized light to right side is called as dextrorotatory and named as *d* (+) lactic acid while other isomer that rotate plane polarized light to left side is called as laevorotatory and named as *l* (-) lactic acid.

The equimolar mixture of dextro and laevo forms is called as racemic mixture. The optical inactivity of racemic mixture is due to external compensation.

Name of Acid	M.P. in K	Density	Specific Rotation $[\alpha]$
(+) lactic acid	299	1.248	+2.24
(-) lactic acid	299	1.248	-2.24

The number of optical isomers increases with increasing number of chiral centers and it is given by formula 2^n , where n indicates number of chiral centers. But this rule is true for compounds having dissimilar chiral centers.

For example, 2,3- dibromo pentane, 2,3- dihydroxy butanoic acid etc.



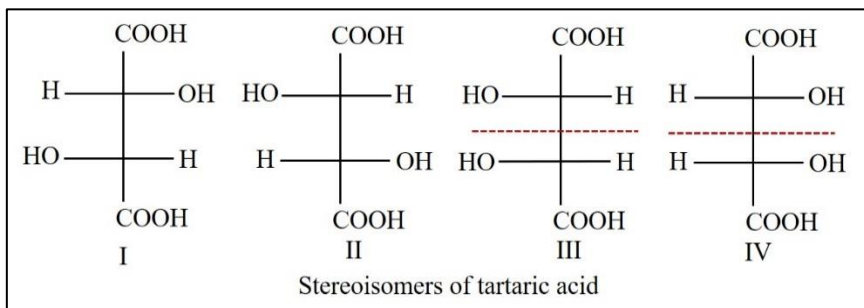
Stereochemistry

Dr. Dattatray R. Chandam

The compounds having even number of identical chiral centers possess less number of stereoisomers than expected.

For example, tartaric acid.

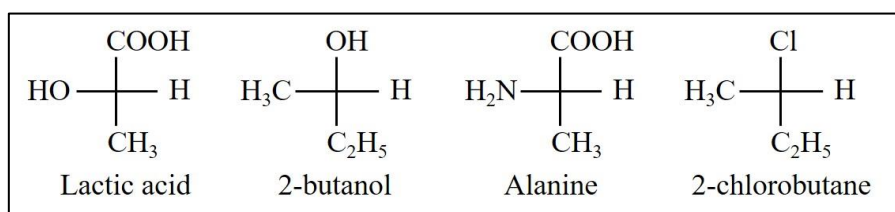
Structure III and IV possess plane of symmetry, therefore, tartaric acid has only 3 stereoisomers i.e., structure I, II and III or IV.



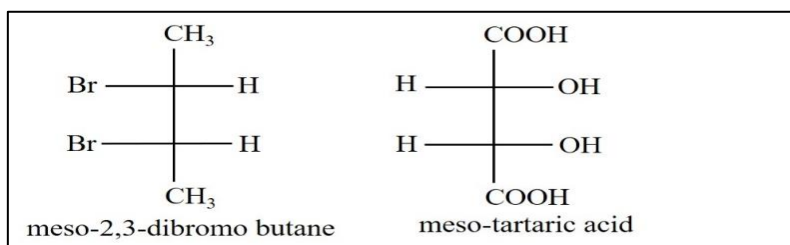
Concept of Chirality

An object which superimposes on its mirror image is called as achiral (or symmetric). An object which does not superimpose on its Mirror image is called as chiral (or asymmetric or dissymmetric). A chiral molecule rotates plane of plane polarized light. **Chirality is structural property of molecule which makes the molecule chiral.** Many organic compounds show optical activity which is unaffected by change in the form. Therefore, chirality is inbuilt in the molecular structure itself. **Louis Pasteur proposed that chirality or dissymmetry is the just and sufficient condition for optical activity.**

The presence of chiral center is potential cause of molecular chirality. A chiral center is sp^3 - hybridized atom linked to four different groups or atoms. It is represented by *. Chiral center is also called as stereocenter. See the examples.



Consider meso-2,3- dibromobutane and meso tartaric acid.

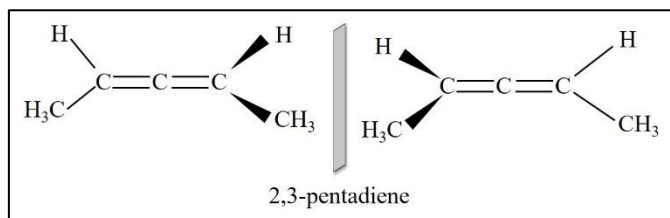


Both meso-2,3- dibromobutane and meso tartaric acid molecules possess two chiral centers, but they are optically inactive. It means that presence of chiral center does not guarantee chirality of the molecule.

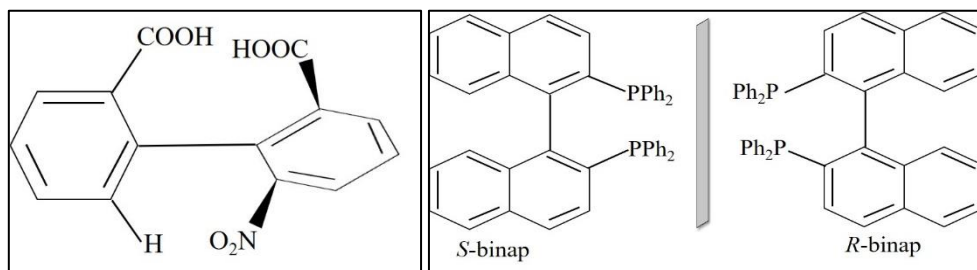
A molecule can be chiral and optically active even if chiral center is absent. It is observed in allenes and substituted biphenyls.

Stereochemistry

Dr. Dattatray R. Chandam



Allene



Substituted Biphenyl

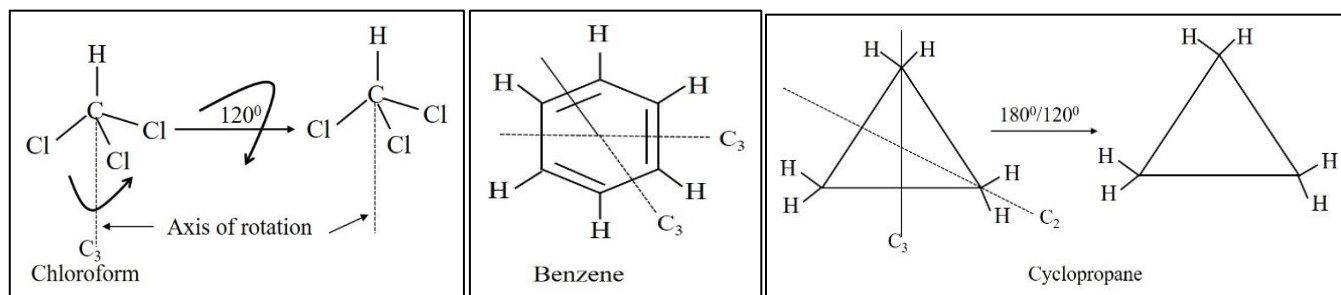
It means that the presence of chiral center is not criteria for molecular chirality. Chirality is related with symmetry or dissymmetry of the molecule rather than presence or absence of chiral center.

Elements of Symmetry.

Four different symmetry elements are used to check chirality of the molecule. Two symmetry operations such as rotation, reflection or combination of both are used to check super imposability of molecule and it's Mirror image. If molecule and its mirror image are non-super imposable, then molecule is chiral and vice versa.

a) Proper axis of symmetry

A molecule is said to have proper axis of symmetry if identical structure is obtained when molecule is rotated around imaginary axis by an angle $360/n$. The imaginary axis is called as n -fold axis of symmetry and represented by C_n . See the examples of Chloroform, Benzene and Cyclopropane.



The rotation of chloroform by angle 120° , rotation of benzene by angle 180° and 60° , rotation of cyclopropane by angle 180° and 120° gives original structures.

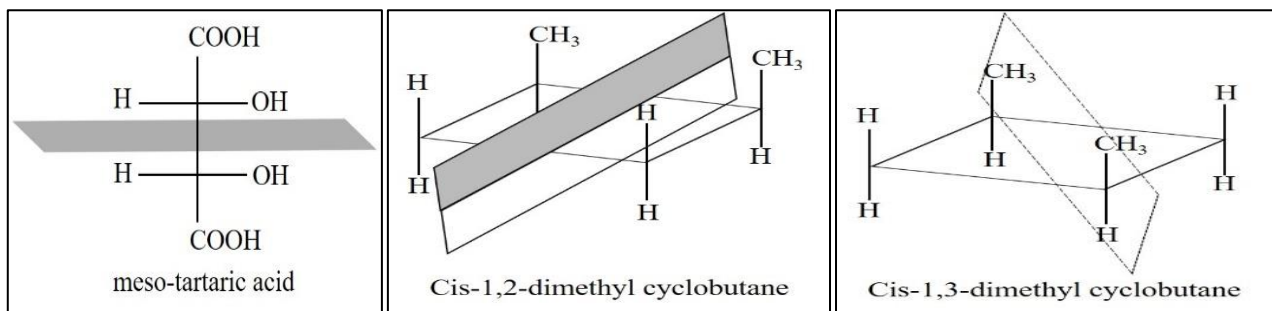
All these compounds possess proper axis of symmetry and they are achiral molecules.

b) Plane of symmetry

A molecule is said to have plane of symmetry if an Imaginary plane divide the molecule into two halves which are mirror images of each other.

Stereochemistry

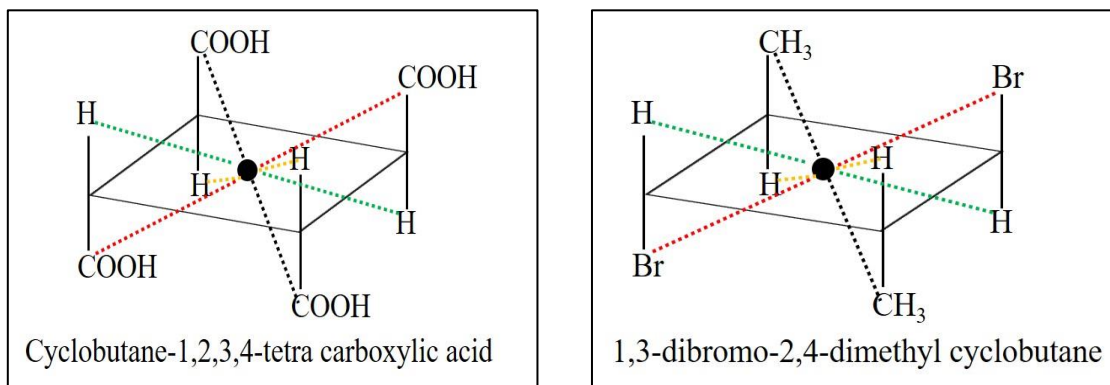
Dr. Dattatray R. Chandam



In meso tartaric acid, plane passes between C2 and C3. In cis-1,2-dimethyl cyclobutane, plane passes through bond C1-C2 and C3-C4. In cis-1,3-dimethyl cyclobutane, two diagonal planes passes through bond C1, C3 and C2, C4.

c) Center of symmetry

A molecule is said to have center of symmetry if molecule possesses an imaginary point from which similar groups stay opposite at equal distance. It is also called inversion center. Molecule can have only one inversion center.

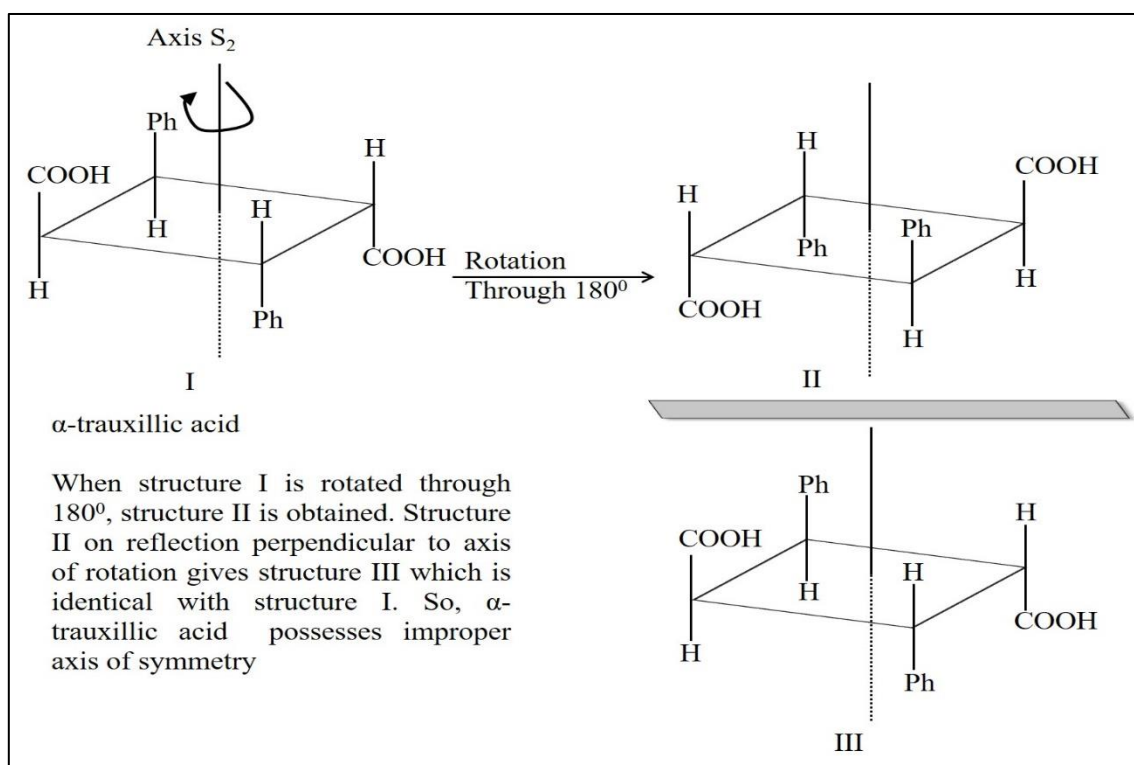
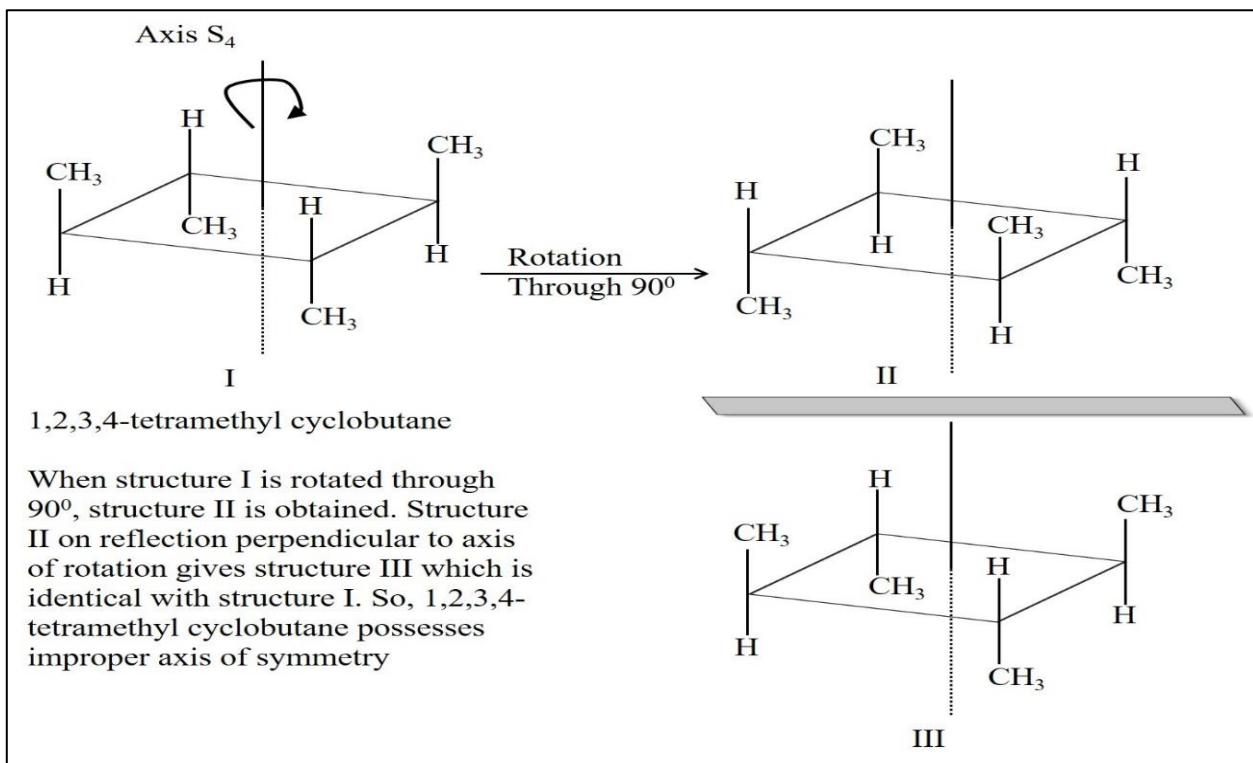


In above examples, similar groups are equal distance but opposite to each other indicated by lines drawn from center.

Generally, even membered ring compounds carry center of symmetry. Molecule with symmetry open also possesses center of symmetry.

d) Improper or alternating axis of symmetry

A molecule is said to have improper axis of symmetry if identical structure is obtained when molecule is rotated around axis by an angle $360/n$ and reflected perpendicular to the axis of rotation. 1,2,3,4-tetramethyl cyclobutane and α -trauxillic acid shows improper axis of symmetry.



A molecule that carries any one of these symmetry elements is said to be achiral. A molecule lacking all four symmetry elements is said to be chiral.

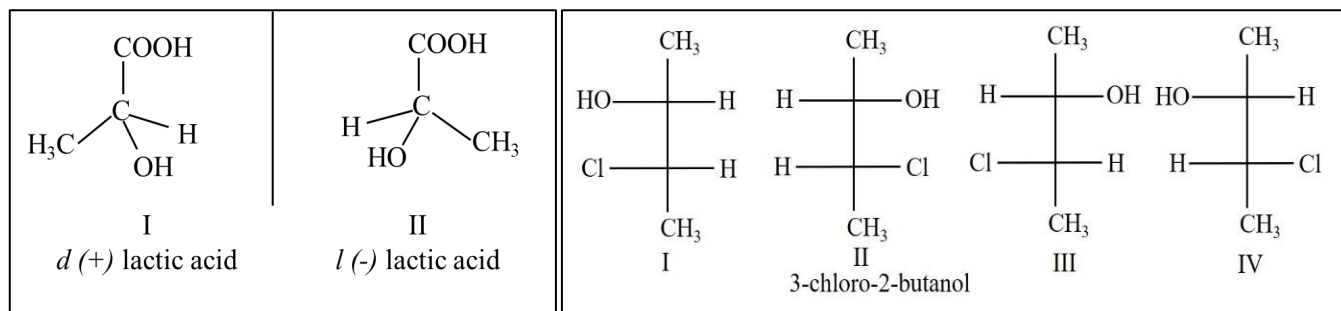
Enantiomers

A pair of stereoisomers which are non-superimposable mirror images of each other are called as enantiomers. They are also called as enantiomorphs or optical antipodes. The structural property of chiral molecules to generate enantiomer is called as enantiomerism.

Chirality is necessary and sufficient condition for existence of enantiomers.

Stereochemistry

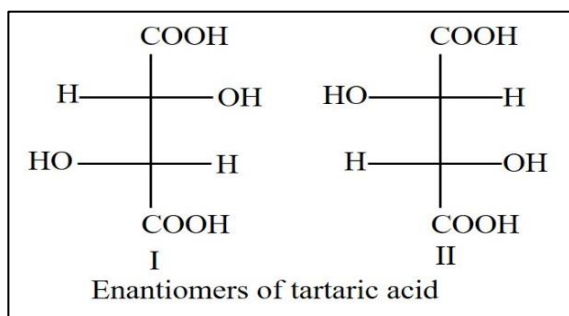
Dr. Dattatray R. Chandam



Lactic acid possesses one pair of enantiomers while 3- chloro-2- butanol possesses two pairs (I & II, III & IV) of enantiomers.

From above examples, it is clear that number of chiral centers increases, pair of enantiomers also increases.

But, in tartaric acid, less number of pair of enantiomers are observed than expected.



It means that compounds with even number of identical chiral centers exist in less number of enantiomers.

Characteristics

- 1) They have object mirror image relationship.
- 2) They are non-superimposable on each other.
- 3) They cannot be interconverted by making and breaking of the bonds.
- 4) They have similar chemical properties but differ in reaction rate towards optically active reagents.
- 5) They have similar physical properties but differ in their action towards plane polarized light. If one is dextrorotatory, the other is laevo rotatory.
- 6) An optically inactive racemic mixture is obtained when equal molar amount of dextro and laevo forms mixed together.
- 7) They form crystals of identical geometry but crystals are mirror images of each other.
- 8) Number of enantiomers increases with increasing number of chiral centers.
- 9) Molecules having n numbers of dissimilar chiral centers exist in 2^{n-1} number of enantiomer pairs.
- 10) Molecules having identical chiral centers exist in less number of enantiomer pairs than expected.

Diastereomers

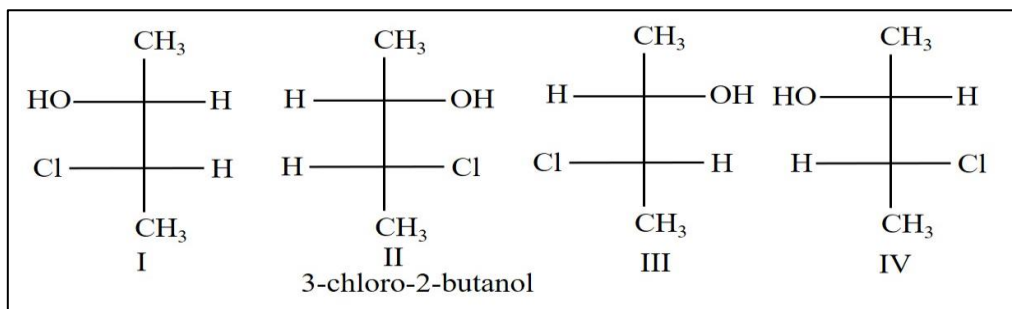
A pair of stereoisomers which are non-superimposable non mirror images of each other are called as **diastereomers**. The structural property of chiral molecules to generate diastereomers is called as diastereomerism.

Molecules having multiple chiral centers shows diastereomers.

3- chloro-2- butanol has two dissimilar chiral centers. It exhibits diastereomerism and gives four pairs of diastereomers.

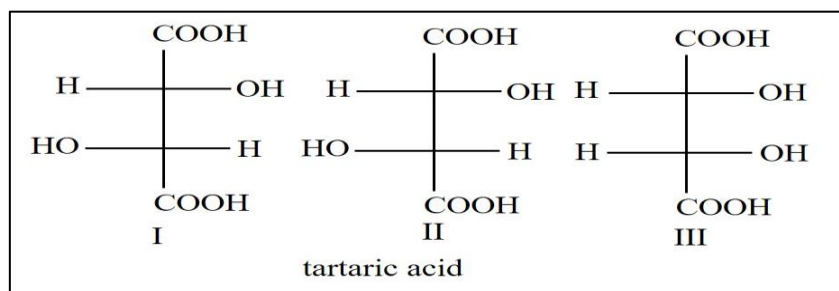
Stereochemistry

Dr. Dattatray R. Chandam



Four pairs i.e. (I & III), (I & IV), (II & III) and (II & IV) are non-superimposable non mirror images of each other, hence, they are pair of diastereomers.

Tartaric acid has two identical chiral centers. It exhibits diastereomerism but gives two pairs (I & III), (II & III) of diastereomers.



It means that compounds with even number of identical chiral centers exist in less number of diastereomers than expected.

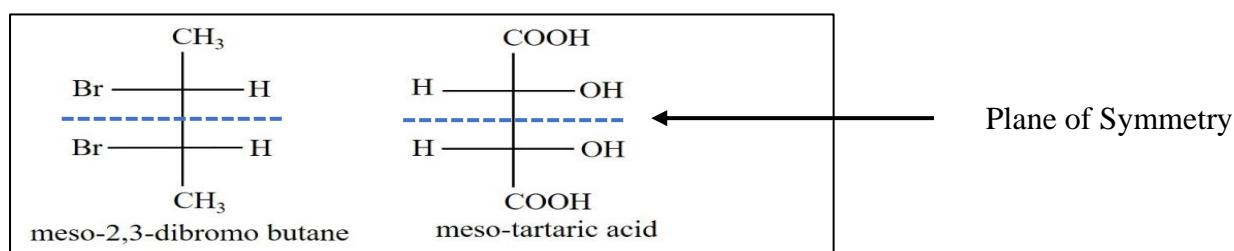
Characteristics

- 1) They do not have object mirror image relationship.
- 2) They are non-superimposable on each other.
- 3) They are observed in molecules with multiple chiral centers.
- 4) Their chemical properties are similar but not identical.
- 5) They have different physical properties.
- 6) Pairs of diastereomers increases with increasing number of chiral centers.
- 7) Molecules having n numbers of dissimilar chiral centers exist in 2^n number of diastereomers pairs.
- 8) Molecules having identical chiral centers exist in less number of diastereomers pairs than expected.

Meso compound

An optically inactive compound carrying multiple chiral centers is called as meso compound.

In 2,3 -dibromo butane and meso tartaric acid, plane of symmetry is present that cuts the molecule in two equal halves which are superimposable mirror images of each other.

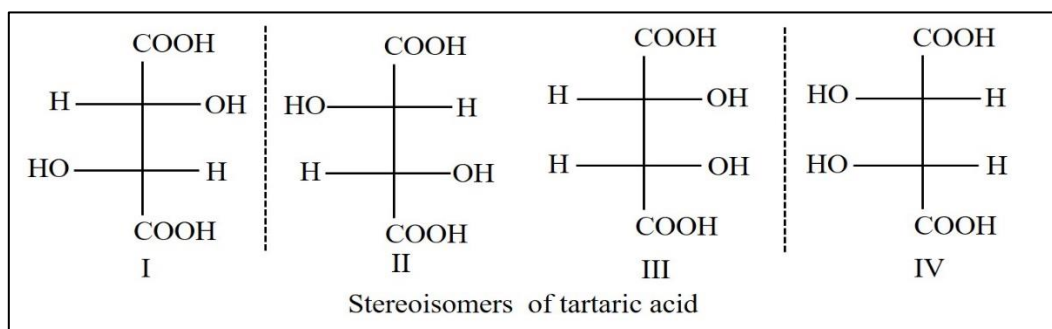


Characteristics

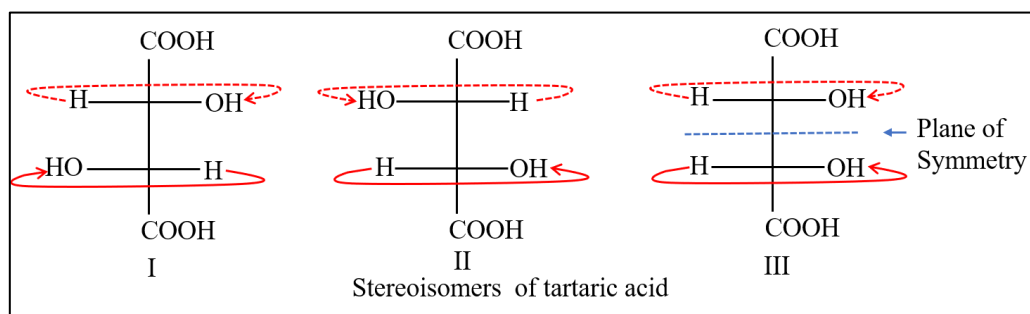
- 1) It carries multiple chiral centers but it is optically inactive.
- 2) It bears plane of symmetry
- 3) It carries even number (more than one) of chiral centers
- 4) Chiral centers in meso compound are identical with same set of groups.
- 5) Optical inactivity of meso compound is due to internal compensation. the right-hand rotation of one half of the molecule is exactly compensated by left-hand rotation of another half of the molecule.

Optical isomerism in tartaric acid

Tartaric acid i.e. 2,3-hydroxy butanedioic acid contains two chiral centers. The groups attached to both chiral centers are same. Theoretically, four stereoisomers are possible which are represented below.



Structure (I) and (II) are non-superimposable mirror images of each other. Therefore, they are enantiomers and optically active. Structure (III) and (IV) are mirror images of each other but turning structure (IV) by 180° , it can be superimposed on structure (III). Therefore, structure (III) and (IV) are identical and they are not enantiomers. It means that tartaric acid exists in only three forms i.e. (+) or d-tartaric acid, (-) or l-tartaric acid and meso tartaric acid.



On the basis of specific rotation four varieties of tartaric acids are recognized. They are as follows.

- 1) (+) or d-tartaric acid: It rotates the plane of plane polarized light to the right or clockwise direction. It is dextrorotatory, $[\alpha] = +12^\circ$.
- 2) (-) or l-tartaric acid: It rotates the plane of plane polarized light to the left or anticlockwise direction. It is laevorotatory, $[\alpha] = -12^\circ$.
- 3) meso tartaric acid: It possesses plane of symmetry between 2nd and 3rd carbon. Both chiral centers are acting in opposite direction but in equal extent. The rotation of one half is compensated by equal and opposite rotation of another half. Therefore, meso tartaric acid is optically inactive due to internal compensation.

Stereochemistry

Dr. Dattatray R. Chandam

4) dl or (+₋) tartaric acid: when equimolar amount of d and l forms of tartaric acid are mixed together, the resulting solution is called as dl tartaric acid. The right-hand rotation of d form is exactly nullified by left-hand rotation of l form. Therefore, dl tartaric acid is optically inactive external compensation.

Structure I is not mirror image of III and non-superimposable also. Structure II is not mirror image of III and non-superimposable also. Therefore, pair (I & III) and (II & III) represents diastereomeric pairs. Thus, tartaric acid has only two pairs of diastereomers which are less than expected.

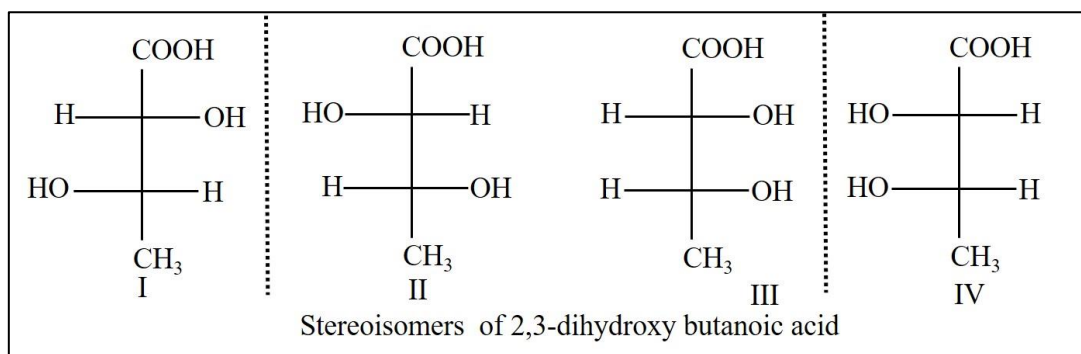
Table: Physical Constant of Tartaric acid

Variety	Melting Point	Density g/mL	Specific Rotation	Solubility (g/100g H ₂ O)
(+) or dextro	443 K	1.76	+12 ⁰	147 (at 293 K)
(-) or laevo	443 K	1.76	-12 ⁰	147 (at 293 K)
Meso	413 K	1.69	0 ⁰	125 (at 288 K)

From about table, it is clear that pair of enantiomers shows similar properties but pair of diastereomers shows different properties.

Optical isomerism in 2,3-dihydroxy butanoic acid

2,3-dihydroxy butanoic acid contains two dissimilar chiral centers. Therefore, four stereoisomers are possible.



Structure II is the mirror image of structure I and they are non-superimposable. Similarly, Structure IV is the mirror image of structure III and they are non-superimposable. Therefore, they are pair of enantiomers. If structure I or III rotate plane of plane polarized light to right or clockwise direction, then structure II or IV will rotate the plane of plane polarized light to left or anticlockwise direction. If structure I and II or III and IV are mixed in a equimolar quantity, corresponding racemic mixture or dl-mixture is obtained.

Now consider pairs as such as structure (I and III), (I and IV), (II and III), (II and IV). The isomers in these pairs are non-superimposable as well as mirror images of each other. Therefore, they are called as pair of diastereomers.

Geometrical Isomerism

The isomerism in which geometrical isomers are formed due to restricted rotation about some bond axis is called as Geometrical Isomerism.

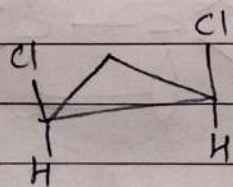
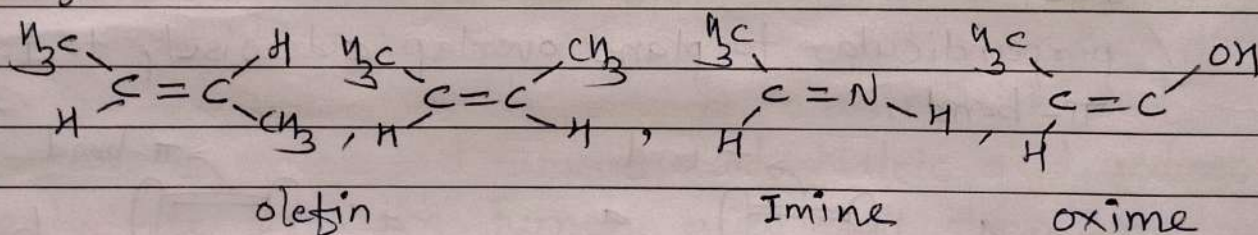
It is one type of diastereomerism and produces distinct and stable isomers. The isomers which are formed due to restricted rotation about some bond axis are called as Geometrical Isomers or cis-trans isomers.

The compound should follow two conditions to show Geometrical isomerism.

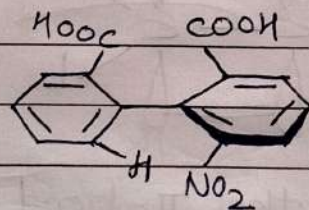
1) Restricted rotation around a bond

The compounds having $>C=C<$ in olefin, $>C=N-$ in imine, oxime, hydrazone shows geometrical isomerism. It is due to restricted rotation about double bond. In cyclic compound, rotation around C-C bond is restricted while in ortho disubstituted biphenyls, this rotation around single bond is restricted due to repulsive strain.

e.g.



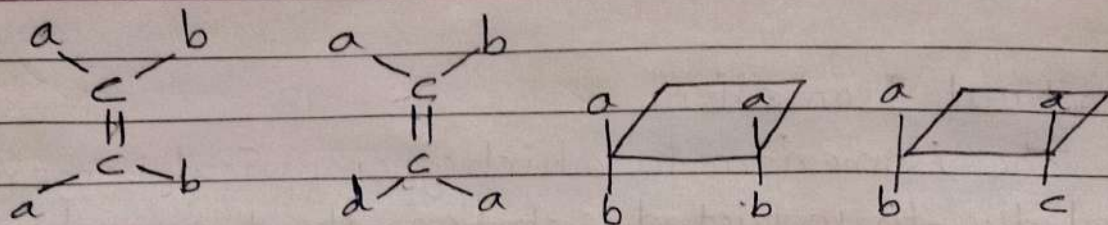
cyclic



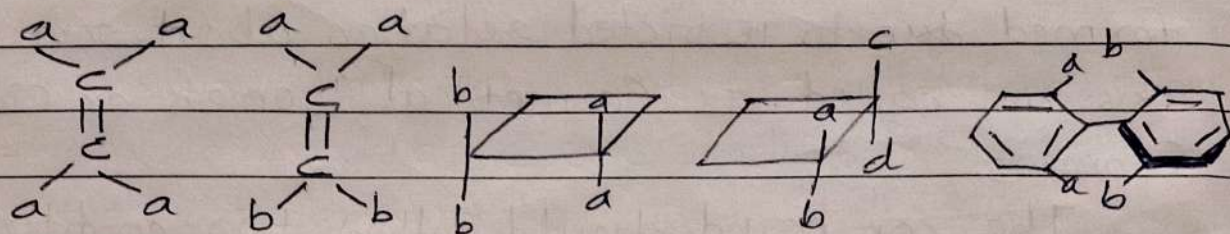
o-disubstituted biphenyl

2) Group requirement at restricted rotation site

- Two atoms between which there is restricted rotation must have at least one identical or both group identical.
- Two groups attached to same carbon should be different.



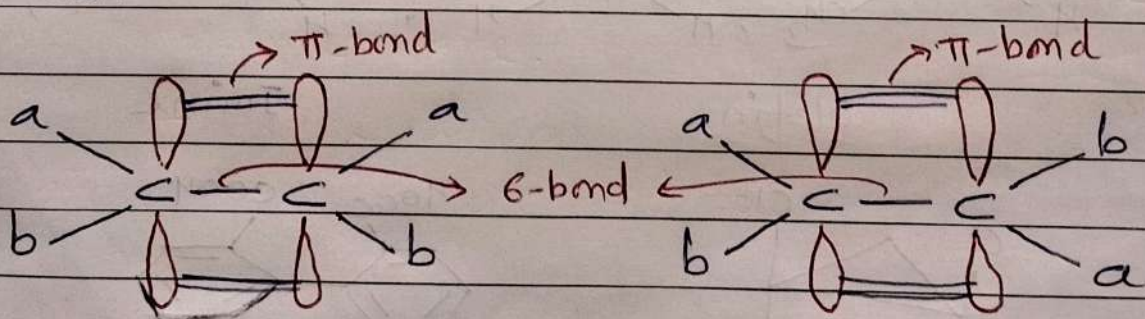
Either one or both group are identical on two carbons and two group on same carbon are different. Therefore, above structure shows Geometrical isomerism.



In above examples, some structures have same group on both carbons or different groups. Therefore, they don't show Geometrical isomerism.

Geometrical Isomerism in $C=C$

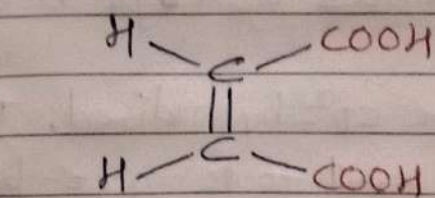
Each Carbon in $C=C$ double bond is sp^2 -hybridised. There are three (3) sp^2 -hybrid orbital and one unhybridised p-orbital on each carbon. sp^2 -hybrid orbitals are used for formation of σ -bond. The p orbitals which are parallel to each other and perpendicular to plane overlap sidewise to form π -bond.



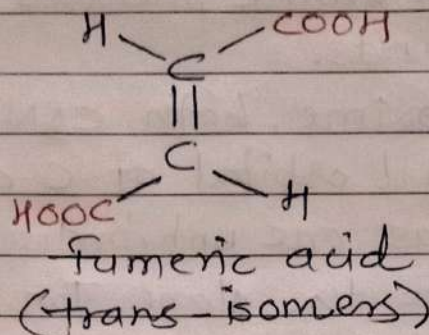
Due to the π -bond, atoms or group of atoms attached to Carbon atoms stay in single plane and position is fixed. The rotation around double bond is restricted as the rotation would break the π -bond.

Geometrical Isomerism in Maleic Acid and Fumaric acid.

Butenedioic acid $[H_2C=CH-COOH]$ ^{has two} shows geometrical isomers i.e. maleic and fumaric acid. These isomers can not be interconverted easily.



Maleic Acid
(Cis-isomer)



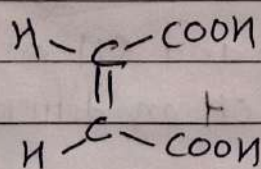
Fumaric acid
(trans-isomer)

In maleic acid, two $-COOH$ group on same side of double bond, hence called as cis-isomers.

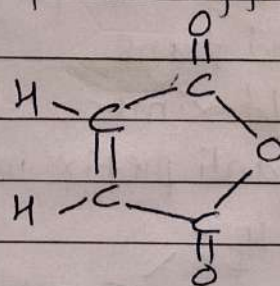
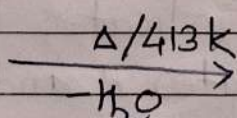
In fumaric acid, two $-COOH$ groups on opposite side of double bond, hence called as trans-isomers.

* Difference in properties.

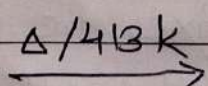
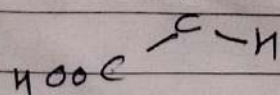
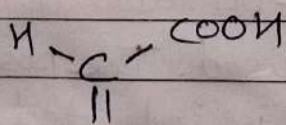
- 1) M.P., B.P. and stability of cis-isomer is lower than that of trans-isomer.
- 2) Density, solubility, dipole moment, refractive index and heat of combustion of cis form is higher than trans.
- 3) Anhydride formation is used to distinguish and separate maleic and fumaric acid. Maleic acid undergo anhydride formation. Fumaric acid don't show anhydride formation because $-COOH$ groups are opposite to each other.



Maleic Acid



Maleic anhydride



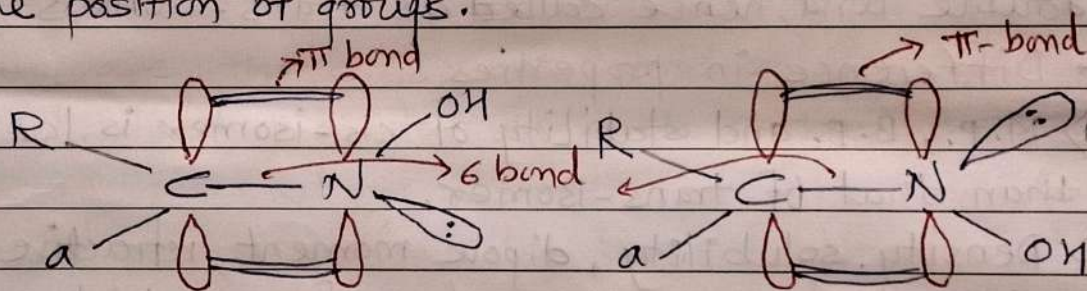
No anhydride formation

4) Spectroscopic Methods are used to distinguish these two forms.

Geometrical Isomerism in Oximes

The condensation of aldehyde or ketone with hydroxyl amine produces oximes as crystalline compounds.

In oxime, both C & N are sp^2 -hybridised. Three sp^2 -hybrid orbital of C are used to form σ -bond whereas one unhybridised p-orbital remain perpendicular to the plane. Two sp^2 -hybrid orbitals of N are used to form σ -bond while third sp^2 -hybrid orbital contains lone pair of electrons. The unhybridised p-orbital present on C and N overlap sideways to form π -bond. The π -bond restricts the rotation and fix the position of groups.

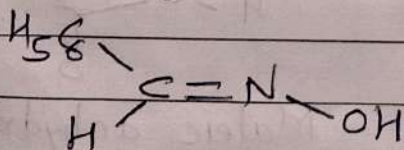


R, OH, a and orbital with lone pair are staying in same plane.

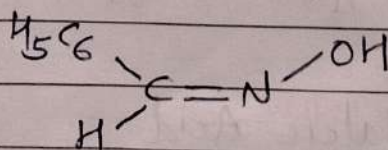
Naming of Oxime isomers

syn and anti prefixes are used for naming instead of cis and trans.

In aldoximes, syn indicates H and OH on same side while anti prefix indicates H and OH on different side.

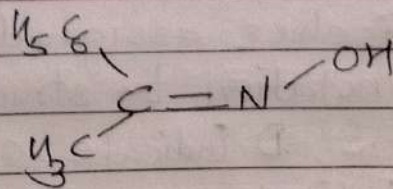
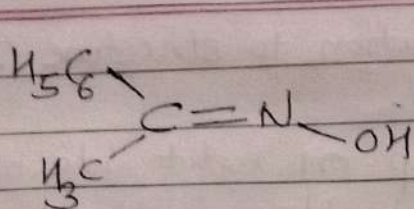


syn-benzaldoxime



anti-benzaldoxime

In ketoxime, both prefixes are used. The position of group with respect to -OH group is indicated by prefixes



syn-methyl phenyl ketoxime
(CH_3 and OH on same side)

syn-phenyl methyl ketoxime
(C_6H_5 and OH on same side)

anti-phenyl methyl ketoxime
(C_6H_5 and OH on opposite side)

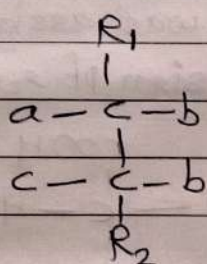
anti-methyl phenyl ketoxime
(CH_3 and OH on opposite side)

syn and anti forms have different physical and chemical properties.

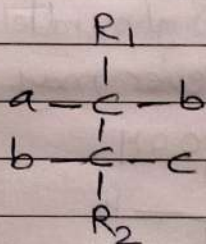
* Nomenclature of Stereoisomers.

1) Threo and Erythro Systems

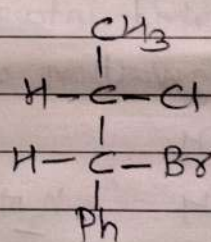
This is used for naming of compounds having two chiral carbons but carrying at least one identical group.



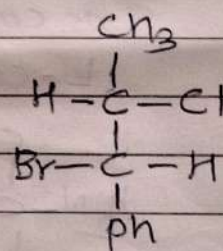
Erythro



Threo



Erythro

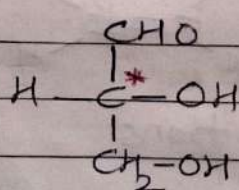


Threo

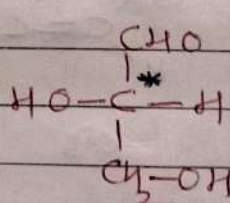
Erythro means like groups on same side
Threo means like groups on opposite side.

2) D and L System

On the basis of position of OH group in Glyceradehyde molecule, Fischer introduced D and L notation.



(I)



(II)

In (I), structure ' OH ' group attached to chiral carbon is on right side.

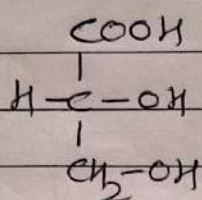
d(+) glyceradehyde l(-) glyceradehyde.

In (II), ' OH ' group attached to left side of chiral carbon. Structure (I) is dextro-rotatory while (II) is laevo-rotatory.

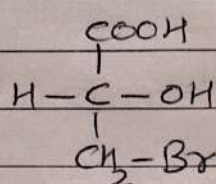
Fischer assigned D notation to structure (I) and L-notation to structure (II).

Here, D indicate OH group on right side of C^*
 L indicate OH group on left side of chiral carbon C^*
 [Do not confuse with d and l because d means dextrorotatory and l means laevorotatory]

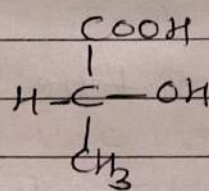
An optically active compound that can be prepared or converted into D-(+) glyceraldehyde was assigned D-configuration whatever may be sign of rotation.



D(-) glyceric acid

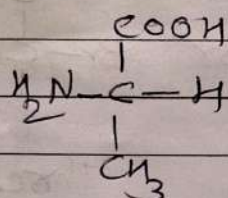


D(-) 3-bromo 2-hydroxy propionic acid

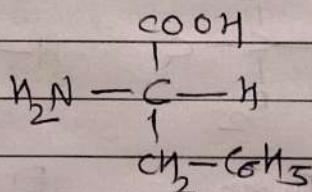


D(-) lactic acid

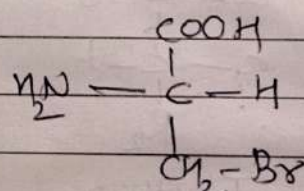
An optically active compound that can be prepared or converted into L(-) glyceraldehyde was assigned L-configuration whatever may be sign of rotation.



L(+) alanine



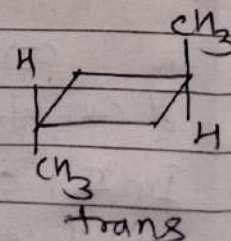
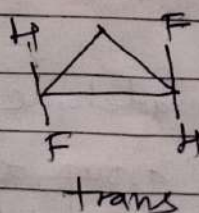
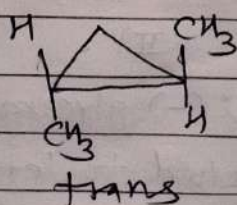
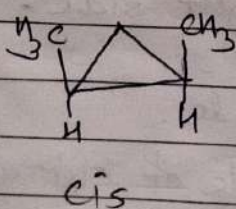
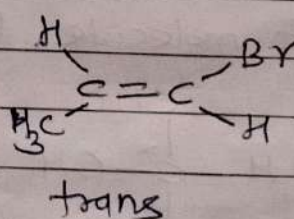
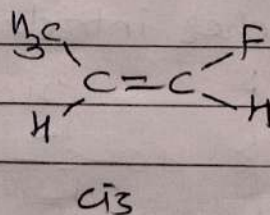
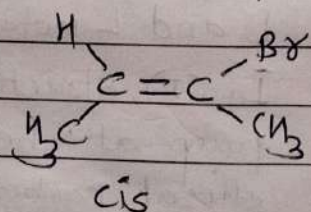
L(-) phenyl alanine



L(-) 3-bromo alanine.

3) Cis-trans system :-

This system is used in geometrical isomers of alkene and cycloalkane.

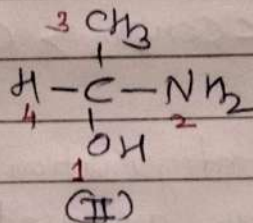
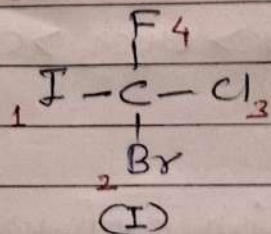


CIP or R/S System :-

Cahn-Ingold-Prelog developed nomenclature system for configurational isomers.

CIP Rules

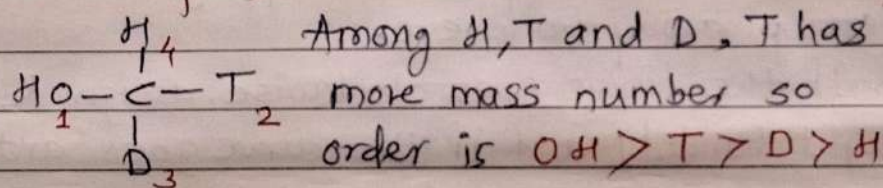
1) Priority assigned to atoms directly attached to chiral carbon based on atomic number.



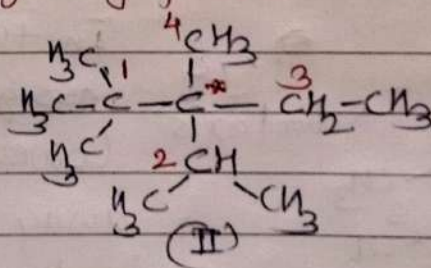
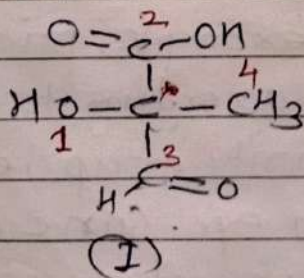
In compound (I), Iodine has highest atomic number so priority to Iodine is 1, so priority order is $\text{I} > \text{Br} > \text{Cl} > \text{F}$

In compound (II), Oxygen has highest atomic number therefore, priority order is $\text{OH} > \text{NH}_2 > \text{CH}_3 > \text{H}$

2) In case of Isotopes, use mass numbers of isotopes.



3) If directly attached atoms are same, next atom is considered for assigning priority.



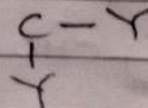
In (I), chiral carbon is attached directly to three carbon, therefore next atom Oxygen and hydrogen is considered for priority, therefore order is $\text{HO} > \text{COOH} > \text{CHO} > \text{CH}_3$

In (II), chiral carbon is attached to four carbon, so next atom either carbon and or Hydrogen is considered.

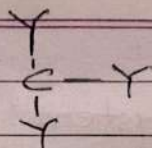
Therefore, order is $(\text{CH}_3)_3\text{C} > (\text{CH}_3)_2\text{CH} > \text{CH}_2\text{CH}_3 > \text{CH}_3$

4) Double bonds must be duplicated and triple bond triplicated.

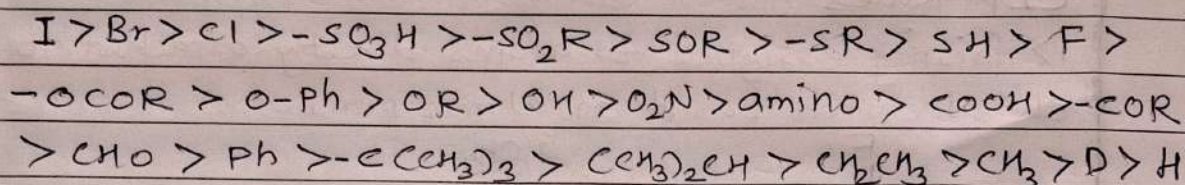
It means $\text{C} = \text{Y}$ become



$-C \equiv Y$ becomes



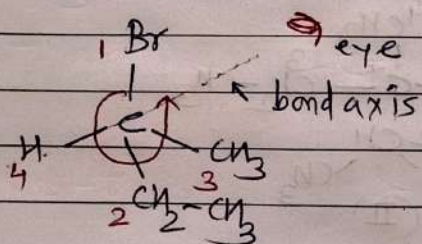
By considering above rules, priority order for different atoms or group of atoms is as follows.



How to Assign configuration?

Following steps are used to assign configuration.

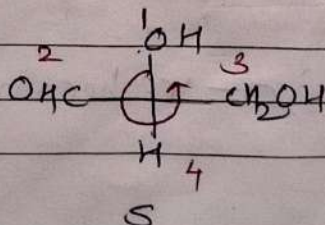
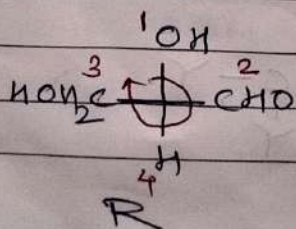
- 1) Assign ~~per~~ priority to four groups attached to chiral carbon (Priority should be 1 to 4)
- 2) Draw a Curve [\curvearrowright] or [\curvearrowleft] in descending priority [i.e. from 1 to 2 to 3] of groups.
- 3) View the compound keeping lowest priority group away from eye.
- 4) If the curve goes clockwise, assign R (Rectus i.e. right handed) and if the curve goes anticlockwise, assign S (sinister, left handed).
- 5) For compounds having multi chiral centres, assign configuration to each chiral centre.



In this example, priority is assigned according to CIP rules. Lowest priority group i.e. H is away from eye. Curve drawn in descending order goes anticlockwise, hence configuration is S.

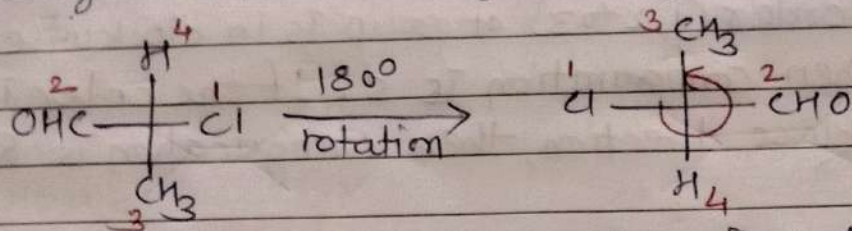
Assigning Configuration in Fischer projection formula Method I

- a) If lowest priority group at the bottom then, clockwise movement from 1 \rightarrow 2 \rightarrow 3 indicates R while anticlockwise movement hints S configuration.



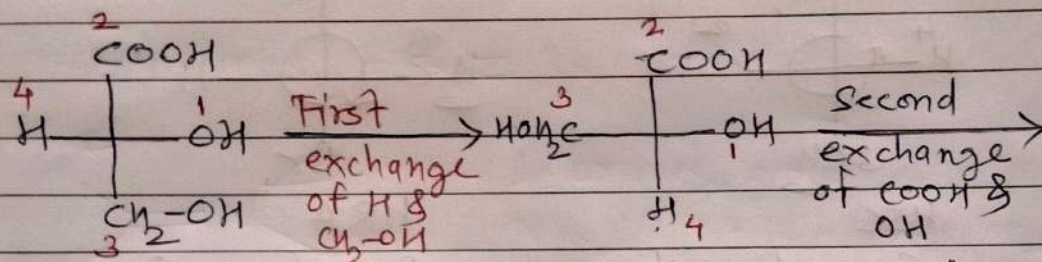
lowest priority group H is at bottom

b) If lowest priority group is at the top, rotate molecule through 180° , then assign configuration.

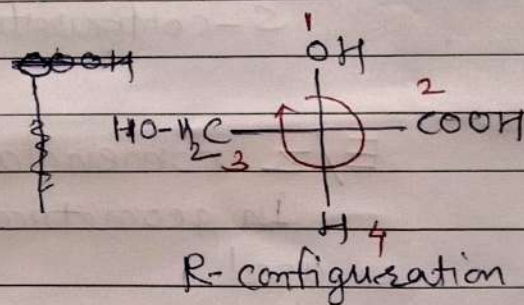


S-configuration

c) If lowest group is at right or left side of horizontal line, then two successive exchanges are carried out to bring lowest priority group at bottom.



Two exchanges are carried out to bring H at the bottom.



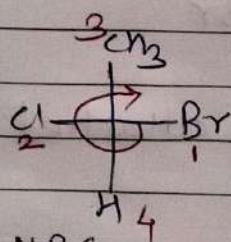
R-configuration

Method 2) Using VRC and HSC rule

a) VRC rule

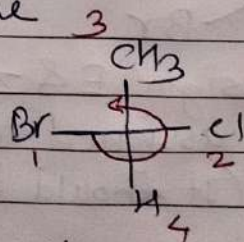
If lowest priority group is on Vertical line and descending priority order (1, 2 to 3) of group is in clockwise direction, then configuration is R. If it is in anticlockwise direction, the configuration is S.

VRC and VSA
 Vertical line
 Rectus clockwise
 Sinister anticlockwise



VRC

R-configuration



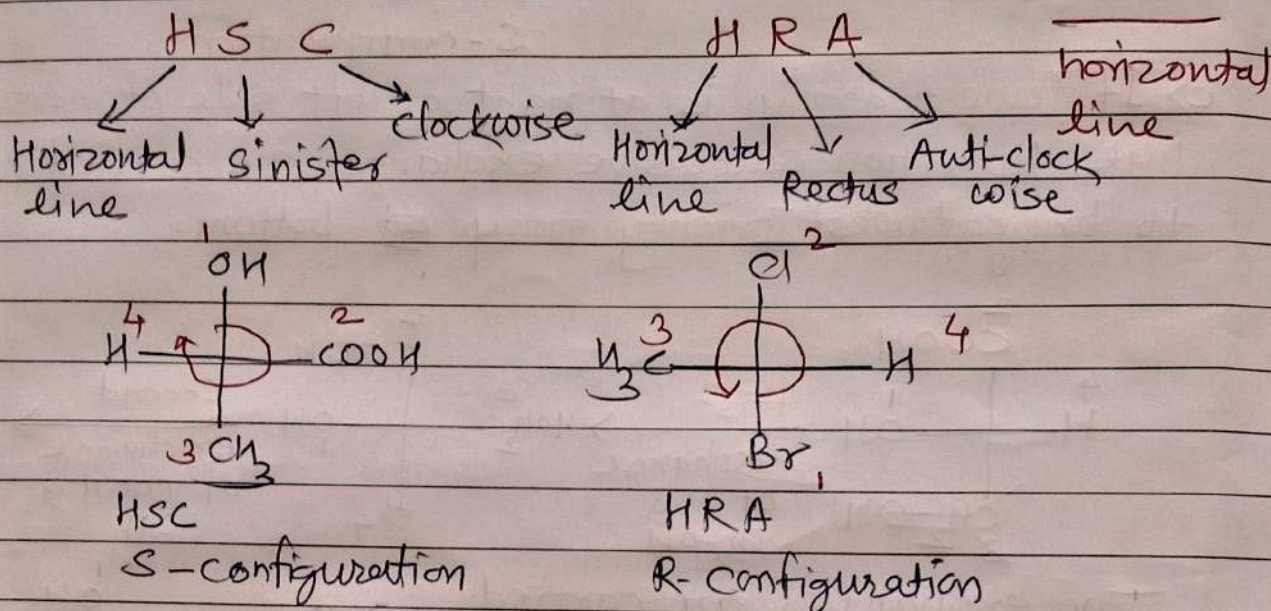
VSA

S-configuration

Vertical line

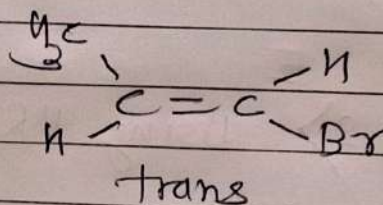
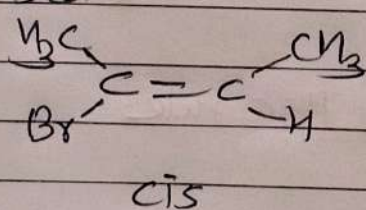
b) HSC Rule

If lowest priority group on Horizontal line, and descending order (1, 2 to 3) of group is in clockwise direction, then configuration is 'S'. If the order is in anticlockwise direction, then configuration is R.



E/Z nomenclature

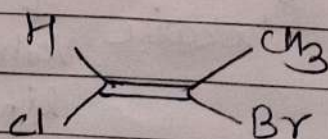
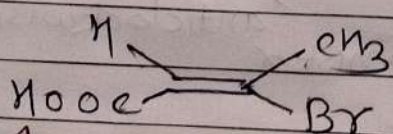
In geometrical isomers, cis and trans naming is used.



But when four different groups are attached, then cis and trans is not adequate. Therefore, in such cases, Blackwood introduced E and Z system.

E means Entgegen → opposite (opposite side)

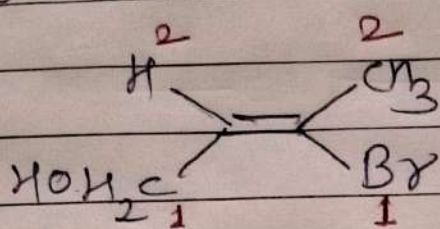
Z means Zusammen → together (same side)



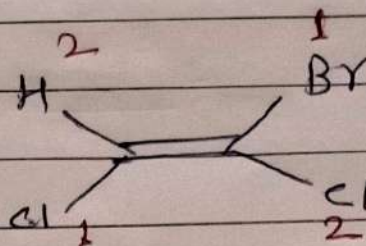
Steps to assign E & Z

1) Priority is assigned to the groups attached to carbon separately (It should be 1 or 2)

2) If same priority group on same side then configuration is Z. If they are on opposite side, then configuration is E

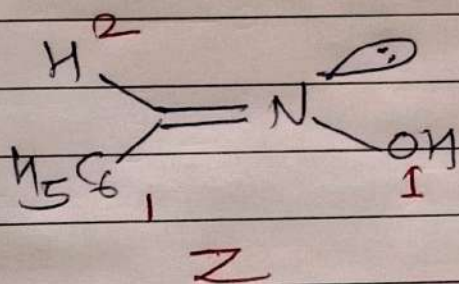


Same priority group on same side of double bond, so configuration is Z



Same priority group on opposite side of double bond, so configuration is E

In case oximes, E & Z is used.



In oximes, group attached to N is OH, it is always having first priority.

